New Robotic Technologies in Cancer Colon Screening

Manfredi, Luigi; Natale, Gianfranco

Published in:
Clinical Cancer Drugs

DOI:
10.2174/2212697X06666181220130020

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Send Orders for Reprints to reprints@benthamscience.ae

Clinical Cancer Drugs, 2018, *5*, 000-000

REVIEW ARTICLE

New Robotic Technologies in Cancer Colon Screening

Luigi Manfredi[1,*] and Gianfranco Natale[2]

[1]*Institute for Medical Science and Technology (IMSaT), University of Dundee, UK;* [2]*Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy*

ARTICLE HISTORY

Received: October 22, 2018
Revised: December 19, 2018
Accepted: December 19, 2018

DOI: 10.2174/2212697X06666181220130020

Abstract: Colorectal cancer (CRC) is the 3rd most common cause of cancer death worldwide. Regular screening of the asymptomatic population can drastically reduce the mortality rate. CRC screening includes several proceedings although the gold standard remains optical colonoscopy (OC), which is unpleasant, causes pain and discomfort. New technologies exemplified by capsule endoscopy (CE) constitute alternative painless solutions and despite their limitations, *e.g.*, passive locomotion and absence of on-board instrumentation, are being increasingly used for CRC screening. Research and development centres are investigating novel advanced robotic technologies for diagnostic and therapeutic use. These include wireless communication, active locomotion, sensors, diagnostic, and therapeutic instruments. This review describes the traditional OC procedure and the existing robotic technologies for CRC.

Keywords: Colonoscopy, robotics, capsule endoscopy, colorectal cancer, cancer screening.

1. INTRODUCTION

Colorectal cancer (CRC) is the 3rd cause of cancer death worldwide in males after lung and prostate cancer, and the 3rd in females after breast and cervix uteri cancer [1]. In 2018, about 1.8 million new cases were reported worldwide (1,006,019 males and 794,958 females) with a mortality of 861,663 (474,606 males and 387,057 females). The reported incidence in affluent Western countries is expected to grow due to the increased longevity in both sexes. Regular screening can detect CRC at an early stage, with a drastic reduction of the mortality by up to 67% [2]. Optical colonoscopy (OC) represents nowadays the gold standard in current use for asymptomatic mass population screening because of its high sensitivity and low false negative rate. It is performed by a fully trained specialised endoscopist by means of a colonoscope. A colonoscope consists of a long flexible tube with a steerable tip, equipped with a camera, suction/ irrigation and instrument channels. A colonoscope is used to inspect the entire colorectal mucosa to detect abnormal lesions; procure tissue biopsy specimens of such lesions for histological examination; provide treatment by removal of polyps or other abnormal lesions; and drug delivery. However, colonoscope insertion up to the caecum (essential for complete colonoscopy) causes discomfort and pain due to tenting of the mesentery and looping. Hence colonoscopy requires sedation. In the last two decades, capsule endoscopy (CE) has been increasingly used for CRC screening. CE colonoscopy screening is completed in 14-70 hours after swallowing PillCam Colon. An external receiver video records the mucosa of the bowel.

The limitations of capsule colonoscopy include lack of active locomotion, transit of the capsule relying on uncontrollable peristalsis and absence of on-board instruments, especially inability to procure biopsies of suspect mucosa lesions. Additionally, it does not allow any therapeutic interventions. Various research groups are investigating novel designs of robotic devices to overcome these limitations.

2. COLONOSCOPY

During the colonoscopy procedure, the colonic wall is examined to identify abnormal lesions. Regular screening by colonoscopy drastically reduces the CRC mortality. For individuals who are considered at average risk of colon cancer, a regular screening program starts at the age of 45. The average risk groups as individual without a personal history of colorectal cancer or certain types of polyps, no family history of CRC; no personal history of inflammatory bowel disease; no confirmed or suspected hereditary CRC syndrome; no personal history of getting radiation to the abdomen or pelvic region to treat prior cancer [3]. Interval cancers are those cancers which are diagnosed after a negative screening test. There is some evidence that the incidence of interval cancers may be reduced by more frequent screening [4].

2.1. Anatomical Considerations

Anatomy represents an important aspect when performing colonoscopic intubation. This invasive procedure may cause pain and discomfort to patients, just due to colon conformation. In this respect, cecal intubation is regarded as the

*Address correspondence to this author at the Institute for Medical Science and Technology (IMSaT), University of Dundee, Wilson House, 1 Wurzburg Loan, Dundee Medipark, Dundee DD2 1FD, UK; Tel: +44 (0) 1382 3881099; E-mail: mail@luigimanfredi.com

2212-697X/18 $58.00+.00

principal goal of a safe and complete colonoscopy, representing an indicator of colonoscopy quality [5]. Indeed, several studies showed a correlation between pain and anatomical colon configuration. In particular, 90% of discomfort coincided with looping colon, whereas only 9% matched with presumed over-insufflation of air. Apart from poor bowel cleanliness, obstructive pathologies and patient discomfort, anatomical factors, including narrow-angle loopings, may contribute to the inability to intubate the caecum [6].

The first difficulty occurs at the beginning of the procedure when, after the rectum, the sigmoid colon develops as a spiral structure over the bladder anteriorly to become the descending colon. Bulges (*haustra coli*) caused by contraction of *taeniae coli* characterize the inner surface of the colon, giving this organ its typical segmented appearance. These pouches, together with splenic and hepatic flexures, can impair the colonoscopy performance. Furthermore, a redundant colon represents one of the main causes of colonoscopy failure. This variation of the colon anatomy occurs when extra loops form, with a colon that is longer than normal. Changes in patient position may improve the configuration of the colon, so helping the advance of the colonoscope tip, according to the experience and skill of the endoscopist [7].

More importantly, rather than to distension, abdominal pain is mainly due to the stretching on the peritoneal ligaments exerted by the colonoscope when advanced to solve eventual loops. In particular, the sigmoid mesentery is stretched, responsible for abdominal discomfort. In women, where the peritoneum undergoes a traction when the colon wraps around the uterus, pain may be more severe. Pulling back on the instrument would relax the tension. In aged or obese patients, the mesentery is lax and stretches more easily, often without pain [7, 8].

2.2. Colon Preparation

The visual inspection of the colonic mucosa requires a colon cleansing preparation (CCP) to remove all faecal material in the colonic lumen. It requires one week of liquid diet and the ingestion of oral cathartic solutions, usually polyethylene glycol. Residual faecal material is a frequent cause of failed colonoscopy. Additional measures are available to prevent residual faecal debris as a cause of failed colonoscopy, *e.g.*, ClearPath^{TM}, a device consisting of two channels: one for irrigation and the other suction. However, this device increases the colonoscope diameter by 6 mm aside from increasing the mechanical stiffness of the colonoscope. Experiments on animals have shown satisfactory results with no damage of the colonic mucosa [8]. Medjet Ltd. (Tel Aviv, Israel), market a soft-tipped catheter device for CCP. It employs a supersonic jet of saline solution mixed with CO_2 to fragment faecal residual debris, which is then removed by suction, deployed through an instrument channel [9].

2.3. Colonoscopy Procedure

The design of a robotic device is based on an initial study and analysis of the standard colonoscopy procedure. This identifies the functionalities that are needed for incorporation in the design of a mini-robotic colonoscope (MRC).

The colonoscope is inserted through the anus and then pushed up to the rectum, recto-sigmoid junction into the colon up to the cecum and the ileo-caecal valve, which marks the entrance of the terminal ileum of the small intestine. The procedure takes about 40 minutes for completion [10]. The surgeon aims to reach the cecum in the shorter time as possible. The orientation of the location is made by visual inspection of the colour and shape of the colonic lumen.

Inspection of the entire colorectal mucosa starts when the cecum is reached, and the entrance of the terminal ileum marked by the ileocaecal valve is identified. Insufflation of the colon with CO_2 is used to expand and stretch the colonic lumen and stretch the colonic walls, thereby enabling insertion of the colonoscope by pushing the flexible endoscope sometimes aided by the application of torque. Pressurised waterjet irrigation is used to clean the camera lens in the event of smudging by mucus of blood. Instrument channels allow the insertion of tools for, *e.g.*, the procurement of a biopsy of polypoid or flat mucosal lesions. Polyps are usually removed (polypectomy) by a special electrosurgical wire loop snares instrument. It is placed over the polyp down to its base and then closed slowly as electrosurgical blender current is applied to prevent coagulation of the blood vessels while the stalk of the polyp is cut. It is important that the detected polyp is removed intact and submitted to detailed histology. If the macroscopic appearance of the polyp suggests possible development of invasive cancer, local endoscopic excision is avoided because of the risk of local recurrence and spread. In such cases, tattooing of the lesions with special ink injected into the base of the polyp is performed. Tattooing enables the surgeon to identify the type of colonic resection required. In general, the biopsy of large polyps (diameter > 1.0 cm) must include the macroscopically abnormal part. Colonoscopy is a difficult procedure which requires a prolonged training to reach proficiency of the endoscopist to practice safe complete colonoscopy. This accounts for its high costs.

2.4. Mechanical Design of a Colonoscope

A colonoscope consists of a flexible inspection tube, about 160 cm long with an external diameter varying from 11 up to 15 mm. The distal tip can be controlled by the operator through a complex twin-wheels-component handle, held and manipulated by the dominant as the endoscope is held and pushed by the non-dominant hand. The tip can be made to bend by manipulating the wheels in two directions, *i.e.*, 2 DOFs, which are defined as roll and pitch. Degrees of freedom (DOF) is a term used in robotics to indicate spatial directions in which a mechanical device is able to move. In this review, the term is used to describe the mechanical properties of a colonoscope and to identify the requirements needed for the design of a robotic device. The rest of the tube is passive and cannot be actively controlled by the operator. The non-dominant hand of the operator holds the colonoscope after it is inserted through the anus into the anal canal to push the flexible colonoscope forwards (1 DOF) and also to torque (rotate) the tube clockwise and anticlockwise (1 DOFs). The total number of DOFs that can be controlled by the operator are 4. The passive tube can be considered as a hyper-redundant structure, with several DOFs, although only 4 can be controlled by the user. This passive tube bends

when it is subjected to a pushing force applied by the operator against the colonic wall, inducing the formation of loops, which by stretching colonic walls and especially the nerves in the mesenteries induce pain and discomfort to the patient [11]. Although anaesthesia can abolish this problem, it is counterproductive to the patient's welfare as pain is an important feedback for the surgeon in avoiding colonic perforation, a potentially life-threatening complication which occurs in 0.6% of cases [12]. A CMOS camera located on the tip of the colonoscope permits imaging and close inspection of the colonic mucosa, with light illumination being provided by super-luminescent LEDs.

3. CE FOR COLONOSCOPY

Capsule Endoscopy (CE) was first presented at the Digestive Disease Week in 2000 held in San Diego, California, USA, by the gastroenterologist Paul Swain, who developed it with Given Imaging, a Yoqneam (Israel) company [13]. CE was CE marked and released in 2001 initially for small bowel endoscopy, subsequently for the oesophagoscopy and finally for colonoscopy. Several other companies followed PillCam SB 3Given Imaging (Ltd, Yogneam, Israel), with their versions of this disruptive technology, including Endocapsule by Olympus America (Inc, Center Valley, Pennsylvana) and MiroCam by Intromedic Company (Ltd, Seoul, South Korea). A Chinese company, Jianshan Science and Technology (Group) Co. Ltd Chongquing, produces the OMOM capsule. The last one has been approved by the State Food and Drug Administration of the People's Republic of China in March 2014, but to date, it has not been approved by the FDA. Its use is limited to China, Southeast Asia and some European countries.

Guidelines on the indications and use of CE have been reported by various clinical societies [14-16]. All the CE devices in current use are wireless but lack active locomotion, relying on physiological peristalsis for transit. However, peristaltic contractile activity varies, and it is thus unreliable. The other major limitation of the current generation of CE devices is their inability to procure biopsies for histological confirmation of the nature of the lesion identified by CE.

Bowel preparation is essential for successful complete colonoscopy, defined as the complete examination of the entire mucosa of the colon and rectum. Following the bowel preparation, the patient has to fast for 8 h to 12 h before the procedure. The bowel preparation consists of ingestion of 1 or 2 L of polyethylene glycol (PEG) over a period of 24 hours before the examination [17].

CE devices are composed of 4 sub-systems: i) disposable or reusable CE with wireless transmission telemetry; ii) wireless receiver array belt and iii) data recorder, both worn by the patient; iv) external workstation with the application software for video and data analysis. CE devices incorporate a localization system which maps the image flow to the position in the intestine for any additional diagnosis or intervention. The location system may use RF (radio frequency), with average localization error up to 13.26 cm^3 [18]. Retention variously reported approximately 2 % can occur during CE screening [19], which would be drastically reduced with active locomotion. In addition, the CE needs to be monitored by the real-time viewing during the first hour to verify that it passed through the stomach into the duodenum (first part of the small bowel). Otherwise, a gastroscopy needs to be performed to place it in the duodenum to ensure that the capsule has enough on-board power to screen all the small bowel.

PillCam Colon 2 was recently approved by the FDA for patients in whom an incomplete colonoscopy was not related to poor bowel preparation. It has two CMOS cameras, front and back, and it is an improved version of the previous PillCam Colon. Advantage includes longer battery life. This feature is obtained by a combination of an extra third-party battery and the use of a sleep mode functionality. The sleep mode consists of a device deactivation for the first 1 h and 30 minutes. This is the average transit time to reach the area of interest. It has a viewing angle of 172° and an algorithm to change the frame rate [20]. The external receiver can analyse the image flow and exchange data with the capsule. This allows the external receiver to detect when the capsule reaches the colon and to adopt a frame rate up to 4 fps. It can also alert the patient if it is retained, when the patient ingests a prokinetic agent, to facilitate transit of the capsule. If the receiver detects that the capsule is retained in the small bowel, the patient is advised to ingest laxative to facilitate the motion.

4. MINI ROBOTIC COLONOSCOPE (MRC)

Although CE devices can perform a painless procedure, they have several issues which limit their use. Sometimes it requires a further investigation by flexible colonoscopy. Research institutes are addressing these limitations by the design of advanced mini robotic colonoscope (MRC). The first challenge encountered in this design is the limited space available inside the colonic lumen. The diameter of the colon varies from 40 up to 90 mm [21]. This limits the use of any off-the-shelf components and the design of miniaturised parts, such as the mechanical frame, the actuation, the sensing and the on-board electronics and wireless communication. An MRC has several components: power management; wireless communication; locomotion; imaging; instrumentations for diagnosis and tissue manipulation; telemetry and user console. Two main approaches are used for the design of an MRC: tethered *vs*. wireless. The advantages and limitation of both designs are discussed in detail in the following sections.

4.1. Tethered MRC

A tether is a combination of wires and/or tubes that extend from the distal part of an MRC till an external console. The primary role of a tether is related to safety. In case of any disfunction on the MRC it can be used to pull it out. In addition, it can help the locomotion solution by contributing with an external force when it is pulled. A tether can incorporate wires for the power supply and for the data transmission. An external power can avoid the need of using internal battery, which limits the autonomy and the performance of the device. The tether can provide a communication channel with high bandwidth to exchange telemetric data and high-quality video streaming with the user console. This will save space avoiding the need for a wireless communication and power unit. Tubes inside the tether can be used to provide

water jet and gas (CO_2) to the tip of the device. Furthermore, these tubes can be used as instrument channels thus allowing the use of standard colonoscopy instrumentations.

The length of the tether is expected to be at least 1.6 meters, with an additional section that extends from the patient to the external console. Its stiffness is related to the material it is composed of, and the number of wires and tubes. The tether external texture and/or coating relates to the friction forces produced between the tether and the colonic wall. Friction is a major drawback of having a tethered device. The force required from the MRC locomotion unit needs to overcome the tether weight but also the friction forces. This can drastically affect the design of the locomotion solution.

4.2. Wireless MRC

Advantages of a tethered MRC represent the limitations in a wireless MRC design. Allocation of space for on-board battery is one of most demanding requirements in the design of an MRC. This is one of the current limitations also in CE. It restricts the fps and quality of the video streaming but also the telemetry. Wireless power can be a solution to this limitation although the low energy efficiency is still an issue in current technology [22]. Miniaturised instruments need to be located on-board with a limitation in the force produced. This also requires a different way to approach a therapeutic procedure that cannot be performed by using traditional instruments. A normal procedure like stretching the colonic wall to improve the inspection of any abnormal lesion requires to find new solutions rather than using air or gas like in a traditional colonoscopy. No need to overcome any force produced by the long tether is the main advantage in the design of a wireless MRC.

4.3. Locomotion

The colonic environment represents a challenge in the design of the locomotion unit. The limit in its available volume requires the use of non-conventional actuation approaches. DC motor and piezo-motor are too heavy, and they require an additional mechanism to increase the output torques or forces, such as a gearbox or spring materials. Compliance and a safe interaction with the surrounding tissue and organs are essential requirements to avoid any damage to the colonic wall. Two are the main methods to design a locomotion unit: on-board and wireless.

4.3.1. On-board Locomotion

The reduction in the size of transducers incurs reduced efficiency. Examples include DC motors, which when available in a large size achieve an efficiency above E_m=90% but with downsizing to millimetres, efficiency can be reduced below E_m=20% (Faulhaber Brushless DC-Servomotor, 3 mm diameter, 8.4 mm in length). In addition, they require a gearbox to increase the output torque with an efficiency below E_g=50%, with a ratio of 125:1. The overall system composed by a DC motor and a gearbox can have an efficiency below 10%, $E=E_m \cdot E_g$. Although this can be a limitation of the design, several MRCs with wheels and legs have been reported [23, 24]. Low energy efficiency requires cooling to dissipate the part of the input energy which is Joule heating. For such small applications, smart materials can provide a valuable alternative solution. Shape Memory Alloy (SMA) has shown some limitations for large actuators because of their low efficiency and slow response time. In contrast, their light weight, high force to weight ratio, and small volume are advantages when a reduced size of just a few millimetres is needed. Their low efficiency below 7% represents a drawback for large actuation but not for small size devices. They can be activated by using external stimulus, *i.e.* light, temperature, magnet field, and chemical stimulus [25]. Limitation in the mechanical bandwidth has been reported for large applications because of the slow time required to dissipate the accumulated heat. In recent studies, Manfredi *et al.* [26-29] reported high mechanical bandwidth for the design of a mini actuator with thin SMA wires, 75μm and 100μm in diameter. Legged MRC has been designed by using SMA [30].

Inch-worm locomotion is one of the most common approaches [31-33]. Having a tether can limit this design. To increase the locomotion propulsion the friction between the MRC and the colonic wall is essential. The friction is related to the weight of the robot and the coefficient friction between the device and the colonic wall, $F_c=P \cdot \mu$. A small robot, due to its low weight, incurs a negligible friction force. This force needs to be higher than the tether weight and friction forces. To increase this F_c, a balloon can be used to apply gas pressure on a wide colon surface [34]. This pressure requires is indicated in 22 mmHg (range 9-57 mm Hg) [35]. Friction around the balloon can be increased by applying patches with special texture [36]. A design that includes two balloons connected together by using a central piston have been proposed for an inch worm soft robot. The locomotion consists of the following recursive 3 steps: i) inflation of the back balloon to anchor the robot; ii) extension of the central piston and then inflation of the front balloon; iii) deflation of the back balloon and contraction of the central piston [37, 31].

Water jet was also investigated to provide propulsion [38]. An external pump controls the water pressure provided by different tubes up to the tip of the device. The device has nozzles that control the direction of the water jet. The activation of each nozzle will control the orientation and propulsion of the device. Water [39] or air [40] pressure was also used to push a balloon with camera and biopsy instruments, which seals the colon and works as a piston. This pressure pushes the balloon forward.

4.3.2. Wireless Locomotion Design

On-board locomotion requires to allocate space for the mechanical solution and additional power supply. This increases the weight and volume of the device. One type of wireless locomotion relies on the use of a magnetic field. Forces are transmitted by using an external magnet to the device that includes small magnets. The external magnetic field can be provided by either a permanent magnet controlled by a robotic arm [41] or it can be generated by using a coil [42]. Permanents magnets, from one to three, are located inside the capsule. This solution will not require the use of an additional power supply and the use of ferromagnetic material can increase the forces. Neodymium is often used for the internal magnet because it is the strongest available in the market. The control and magnitude of the magnetic field

needed to generate forces and torques for the locomotion propulsion is essential for a magnetic device. This defines the size of the internal permanent magnet. The external magnet source requires careful selection for precise control of the locomotion. The use of an external permanent magnet can limit the dexterity in the control of the device. This is related to the orientation of the magnetic field that controls the applied force. Most of the solutions with external magnets produce a force with a vector component that attracts the device to the external magnet [43], thus against the colonic wall. This force needs to be estimated because if too high, it can stretch the colonic wall and cause pain. In addition, it can also create a friction force opposing the propelling force. A magnetic field produced by an external coil can increase the precision of the control. MRI has been used to control the external magnetic field [44]. Limitation of this approach is the high cost in the design of an external active magnet or only by using an MRI.

4.4. Vision Unit

The imaging unit is essential for the inspection of the colonic wall. It includes an image sensor with lens, illumination and chip for video flow compression. A high-resolution imaging unit reduces the false negative rate [45]. In the current colonoscopy and in most of the MRC the imaging unit represents a feedback for the user control. A closed-loop can be implemented by using machine learning algorithms that detect the colon lumen and stabilise the capsule orientation and position [46]. CMOS and CCD can be used for the image sensor. Lower power consumption, higher integration capability, and controllability make the CMOS technology the best option. The CMOS and the lens define the field of view (FOV) up to 180° for a traditional colonoscope [40]. The compression algorithm can reduce the bandwidth for the data communication, essential for the wireless camera. The compression rate is a compromise between the power consumption and the bandwidth. Additional inertial sensors can be integrated in the image unit to filter the tremor and improve the video streaming quality [47].

4.5. Telemetry

A wireless MRC requires a wireless communication to allow image and data streaming to the console for the user control. Low power consumption and reliable data link are essential requirements for the telemetry unit. Radio frequency is the commonest technology used in CE and MRC. [48] reported a design that uses 5.2 mW, a data rate of 2.7 Mb/s at 403-443 MHz. [49] reported power consumption of 2.5 mW and a data rate of 10 Mb/s. Thonè *et al.* [50] reported a telemetry chip with a power consumption of 2 mW and a data rate of 2 Mb/s at 144 MHz.

The human body communication uses the body tissue to transmit data. It has a low power consumption, good communication performance and a reliable data link [51]. The MiroCam is the first CE capsule in the market that includes this technology [52].

4.6. Power

The power supply is one of the current limitations in the design of a wireless MRC. On-board power unit uses silver-oxide coin batteries because they are the only technology approved for clinical use. However, other solutions have a higher energy density [53]. Lithium ion polymer (LiPo), thin-film are other technologies with higher power density. Wireless power by using external magnetic field generated by a solenoid coil power can be an alternative solution [16]. On board batteries have a limited pick current, which limits the output locomotion power. An energy buffer can be used to provide higher electrical current by using an electric double-layer capacitor [54].

Algorithms are used to save energy, *i.e.* by changing the imaging frame rate in relation to the device speed, sleep mode when any action is not required, and low power consumption compression algorithm for the video streaming [55].

4.7. Localisation

The localisation unit identifies the position of the MRC inside the colon for the navigation as well as the identification of any abnormal lesion for future treatment or additional diagnosis. The error of the resolution of the position defines the performance. Radio frequency triangulation is a technology solution with low resolution. Fisher *et al.* [50] reported an average error below 38 mm. A magnetic tracking can achieve a position of 3.3 mm [51]. This technology is affected by the use of any magnet inside or outside the MRC. This limits the locomotion solution design. Ultrasound has been used as localisation technology but with a low-resolution tracking [56]

5. COSTS AND BUDGET

The cost of a traditional complete colonoscopy ranges from $ 800 to $ 4000. CE is much cheaper with a cost around $ 500. An additional cost for a colonoscopy is the training required for the colonoscopist to reach proficiency. The time needed to perform the procedure is included in the running costs.

MRC has the potential to reduce substantially the cost of mass screening for CRC in the adult asymptomatic population. However, MRC will only outperform and replace flexible colonoscopy when it progresses to the stage when key functions exemplified by biopsy procurement and the ability to stop bleeding are included in the device. An MRC can be used by nurses or trained technicians on several patients, with a medical specialist being present to supervise from a control centre several procedures being simultaneously carried out. The training will be limited to the use of the console interface and for the technician for the periodical maintenance. As the MRC colonoscopy will be painless, no sedation will be needed, and the screening interval can be reduced, lowering the incidence of the interval cancers. However, the construction and production of an MRC require the use of miniaturised components and expensive assembling and testing technologies. Regular maintenance will require special training for the technician employed in a hospital. The need for FDA approval or CE mark will also increase the final market cost. All these costs need to be addressed since the beginning of the design of a new concept by the research institutes. Providing a new technology that will not be cost effective will limit its application.

CONCLUSION

This review describes the current technology for CRC screening with the advantages and limitations. It describes the research challenges in the design of new technologies for mini- robotic colonoscopes. These frontier technologies aim to replace the current colonoscope with a solution that is painless and cost effective with the scope of reducing the cancer mortality through early detection of precancerous lesions of early stage curable cancer. A multi-disciplinary approach is required to face these challenges. Expertise in different engineering areas, such as electronics, mechanics, telecommunications, advanced materials, *etc*., need to converge to provide a combined solution. Furthermore, it will also require a scientific bridge connection with medical science to understand the environment where this device works and what the medical need is to improve disease management. With the advances in autonomous devices, one day the procedure will be fully autonomous with a mini-robot that will be able to perform the screening and detect abnormal lesions, for example by using machine learning [56] and with an autonomous locomotion control. The screening data will be globally shared in a cloud solution to involve experts from different institutes when an issue is encountered during the screening. Training of the colonoscopist and the nurse will be drastically reduced because of the high level of autonomy that will be incorporated into the MRC.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2018.

[2] Hamashima C, Shabana M, Okada K, Okamoto M, Osaki Y. Mortality reduction from gastric cancer by endoscopic and radiographic screening. Cancer Science. 2015; 106(12): 1744-1749.

[3] https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/acs-recommendations.html

[4] Pate SG, Ahnen DJ. Prevention of interval colorectal cancers: what every clinician needs to know. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 2014; 12, 7-15.

[5] Morini S, Zullo A, Hassan C, Lorenzetti R, Campo SM. Endoscopic management of failed colonoscopy in clinical practice: to change endoscopist, instrument, or both? International Journal of Colorectal Disease 2011; Jan;26(1):103-8.

[6] Tumino E, Parisi G, Bertoni M, Bertini M, Metrangolo S, Ierardi E, Cervelli R, Bresci G, Sacco R. Use of robotic colonoscopy in patients with previous incomplete colonoscopy. European Review for Medical and Pharmacological Sciences 2017; 21(4):819-826.

[7] Waye JD, Thomas-Gibson S. How I do colonoscopy. Gastrointest Endosc. 2018; 87(3): 621-624.

[8] Moshkowitz M, Hirsch Y, Carmel I, *et al.* A novel device for rapid cleaning of poorly prepared colons. Endoscopy 2010; 42(10): 834-6

[9] Kiesslich R, Schuster N, Hoffman A, *et al.* MedJet - a new CO2-based disposable cleaning device allows safe and effective bowel cleansing during colonoscopy: a pilot study. Endoscopy 2012; 44(8):767-71.

[10] Klare P, Ascher S, Hapfelmeier A, Wolf P, Beitz A, Schmid RM, von Delius S. Patient age and duration of colonoscopy are predictors for adenoma detection in both proximal and distal colon. World Journal of Gastroenterology, 2015; 21: 525-532.

[11] Loeve AJ, Fockens P, Breedveld P. Mechanical analysis of insertion problems and pain during colonoscopy: why highly skill-dependent colonoscopy routines are necessary in the first place... and how they may be avoided, Canadian journal of gastroenterology. Journal Canadien de Gastroenterologie, 2013; 27: 293-302.

[12] Polter DE. Risk of colon perforation during colonoscopy at Baylor University Medical Center. Proceedings (Baylor University. Medical Center), 2015; 28: 3-6.

[13] Moglia A, Menciassi A, Dario P, Cuschieri A. Capsule endoscopy: progress update and challenges ahead. Nature reviews. Gastroenterology & Hepatology, 2009; 6: 353-362.

[14] Mishkin DS, Chuttani R, Croffie J, Disario J, Liu J, Shah R, Somogyi L, Tierney W, Song LMWK, Petersen BT. Technology Assessment Committee, A. S. f. G. E., ASGE Technology Status Evaluation Report: wireless capsule endoscopy. Gastrointestinal Endoscopy, 2006; 63: 539-545.

[15] Ontario HQ. Clinical utility of serologic testing for celiac disease in ontario: an evidence-based analysis, Ontario health technology assessment series, 2010; 10: 1-111.

[16] Argüelles-Arias F, Donat E, Fernández-Urien I, Alberca F, Argüelles-Martín F, Martínez MJ, Molina M, Varea V, Herrerías-Gutiérrez JM, Ribes-Koninckx C. Guideline for wireless capsule endoscopy in children and adolescents: A consensus document by the SEGHNP (Spanish Society for Pediatric Gastroenterology, Hepatology, and Nutrition) and the SEPD (Spanish Society for Digestive Diseases), Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva, 2015; 107: 714-731.

[17] Mergener K, Ponchon T, Gralnek I, Pennazio M, Gay G, Selby W, Seidman EG, Cellier C, Murray J, de Franchis R, Rösch T, Lewis BS. Literature review and recommendations for clinical application of small-bowel capsule endoscopy, based on a panel discussion by international experts. Consensus statements for small-bowel capsule endoscopy, 2006/2007, Endoscopy, 2007; 39: 895-909.

[18] Bandorski D, Kurniawan N, Baltes P, Hoeltgen R, Hecker M, Stunder D, Keuchel M. Contraindications for video capsule endoscopy. World Journal of Gastroenterology 2016; 22: 9898-9908.

[19] Rondonotti E. Capsule retention: prevention, diagnosis and management, Annals of Translational Medicine 2017; 5: 198.

[20] Adler SN, Metzger YC. PillCam COLON capsule endoscopy: recent advances and new insights. Therapeutic advances in gastroenterology 2011; 4: 265-268.

[21] Horton KM, Corl FM, Fishman EK. CT evaluation of the colon: inflammatory disease, Radiographics: a review publication of the Radiological Society of North America, Inc 2000; 20: 399-418.

[22] Basar MR, Ahmad MY, Cho J, Ibrahim F. Application of wireless power transmission systems in wireless capsule endoscopy: an overview. Sensors (Basel, Switzerland) 2014; 14: 10929-10951.

[23] Sendoh M, Ishiyama K, Arai KI. Fabrication of magnetic actuator for use in a capsule endoscope. IEEE Transactions on Magnetics 2003: 39(5): 3232–3234.

[24] Vu H, Echigo T, Sagawa R, Yagi K, Shiba M, Higuchi K, Arakawa T, Yagi Y. Detection of contractions in adaptive transit time of the small bowel from wireless capsule endoscopy videos. Computers in Biology and Medicine 2009; 39(1): 16–26.

[25] Mahtabi MJ, Shamsaei N, Mitchell MR. Fatigue of Nitinol: The state-of-the-art and ongoing challenges. Journal of the Mechanical Behavior of Biomedical Materials 2015; 50: 228-254.

[26] Manfredi L, Huan Y, Cuschieri. A. Low power consumption mini rotary actuator with SMA wires. Smart Materials and Structure 2017; 26: 115003.

[27] Manfredi L, Cuschieri A. Complaint Actuator. GB Patent Application GB201407490D0, 11 June 2014, US, Patent Application US20170051729A1, 23 February 2017.

[28] Manfredi L, Cuschieri A. Design of a 2 DOFs Mini Hollow Joint Actuated with SMA Wires. Materials 2018; 11: 2014.

[29] Manfredi L, Cuschieri A. Design of a 2 DOFs Mini Hollow Joint Actuated with SMA Wires. Materials 2018; 11(10).

[30] Cheung E, Karagozler ME, Park S, Kim B, Sitti M. A new endo-

scopic microcapsule robot using beetle inspired microfibrillar adhesives, Proceedings, 2005 IEEE/ASME International Conference on Advanced Intelligent Mechatronics, Monterey, CA, 2005: 551-557.

[31] Gao J, Yan G, Wang Z, Xu F, Wang W, Jiang P, Liu D. Locomotion enhancement of an inchworm-like capsule robot using long contact devices. The international journal of medical robotics + computer assisted surgery: MRCAS 2017; 13.

[32] Hosokawa D, Ishikawa T, Morikawa H, Imai Y, Yamaguchi T. Development of a biologically inspired locomotion system for a capsule endoscope. The international journal of medical robotics + computer assisted surgery: MRCAS 2009; 5: 471-478

[33] Kim B, Park S, Jee CY, Yoon SJ. An earthworm-like locomotive mechanism for capsule endoscopes. IEEE/RSJ International Conference on Intelligent Robots and Systems, Edmonton, Alta., 2005: 2997-3002.

[34] Breedveld P. Development of a Rolling Stent Endoscope. The First IEEE/RAS-EMBS International Conference on Biomedical Robotics and Biomechatronics. BioRob 2006., Pisa, 2006; 921-926.

[35] Committee GTA, Maple JT, Banerjee S, Barth BA, Bhat YM, Desilets DJ, Gottlieb KT, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Song LMWK, Rodriguez SA. Methods of luminal distention for colonoscopy, Gastrointestinal Endoscopy 2013: 77: 519-525.

[36] Chen W, Yan G, He S, Ke Q, Wang Z, Liu H, Jiang P. Wireless powered capsule endoscopy for colon diagnosis and treatment. Physiological Measurement 2013: 34: 1545-1561.

[37] Wang K, Ge Y, Jin X. A micro soft robot using inner air transferring for colonoscopy, IEEE International Conference on Robotics and Biomimetics (ROBIO), Shenzhen 2013: 1556-1561.

[38] Campisano F, Gramuglia F, Dawson IR, Obstein KL, Misra S, De Momi E, Valdastri P. Water Jet Actuation for Ultra-low Cost Endoscopy: Characterization of Miniature Nozzles Fabricated by Rapid Prototyping, Procedia Engineering 2016: 16:388-391.

[39] Coleman SA, Tapia-Siles SC, Pakleppa M, Vorstius JB, Keatch RP, Tang B, Cuschieri A. A hydraulically driven colonoscope. Surgical Endoscopy 2016; 30: 4515-4524

[40] http://www.giview.com/

[41] Ciuti G, Donlin R, Valdastri P, Arezzo A, Menciassi, A, Morino M, Dario P. Robotic *versus* manual control in magnetic steering of an endoscopic capsule. Endoscopy, 2010; 42: 148-152.

[42] Rey JF, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, Aihara H, Pangtay I, Hibi T, Kudo S, Tajiri H. Feasibility of stomach exploration with a guided capsule endoscope. Endoscopy 2010; 42: 541-545.

[43] Slawinski PR, Taddese AZ, Musto KB, Obstein KL, Valdastri P. Autonomous Retroflexion of a Magnetic Flexible Endoscope, IEEE Robotics and Automation Letters. 2017; 2:1352-1359.

[44] Lorenzo-Zúñiga V, de Vega VM, Domènech E, Cabré, E, Mañosa M, Boix J. Impact of capsule endoscopy findings in the management of Crohn's Disease. Digestive Diseases and Sciences 2010; 55: 411-414.

[45] Zabulis X, Argyros AA, Tsakiris DP. Lumen detection for capsule endoscopy, IEEE/RSJ International Conference on Intelligent Robots and Systems, Nice 2008; 3921-3926.

[46] Wang Q, Khanicheh A, Leiner D, Shafer D, Zobel J. Endoscope field of view measurement. Biomedical Optics Express 2017; 8:1441-1454.

[47] Lee HC, Jung CW, Kim HC. Real-time endoscopic image orientation correction system using an accelerometer and gyrosensor. PloS One 2017; 12.

[48] Rohit C *et al*. Localization of an RF source inside the Human body for Wireless Capsule Endoscopy. BODYNETS 2013.

[49] Gao Y, Diao S, Ang CW, Zheng Y, Yuan X. Low power ultra-wideband wireless telemetry system for capsule endoscopy application, Robotics Automation and Mechatronics (RAM), IEEE Conference on, 2010; 96-99.

[50] Fischer D, Schreiber R, Levi D, Eliakim R. "Capsule endoscopy: The localization system. Gastrointest. Endosc. Clin. N. Amer. 2004; 14: 25–31.

[51] Zhao JF, Chen XM, Liang BD, Chen QX. A Review on Human Body Communication: Signal Propagation Model, Communication Performance, and Experimental Issues. Wireless Communications and Mobile Computing 2017:15.

[52] Kim HM, Kim YJ, Kim HJ, Park S, Park JY, Shin SK, Cheon JH, Lee SK, Lee YC, Park SW, Bang S, Song SY. A Pilot Study of Sequential Capsule Endoscopy Using MiroCam and PillCam SB Devices with Different Transmission Technologies. Gut and Liver 2010; 4: 192-200

[53] Layton BE. A comparison of energy densities of prevalent energy sources in units of joules per cubic meter. International Journal of Green Energy, Taylor & Francis 2008; 5: 438-455.

[54] Sharma P, Bhatti T. A review on electrochemical double-layer capacitors. Energy conversion and management, Elsevier 2010; 51: 2901-2912.

[55] P Turcza, M Duplaga. Low-Power Image Compression for Wireless Capsule Endoscopy. IEEE International Workshop on Imaging Systems and Techniques, Krakow 2007; 1-4.

[56] Fischer D, Schreiber R, Levi D, Eliakim R. Capsule endoscopy: the localization system. Gastrointestinal Endoscopy Clinics, Elsevier 2004; 14: 25-31

[57] Manivannan S, Wang R, Trucco E, Hood A. Automatic normal-abnormal video frame classification for colonoscopy. IEEE 10th International Symposium on Biomedical Imaging, San Francisco, CA 2013; 644-647.